Status of the claims

Claims 116-131, 138-141, 146-151, 160, 164-166, 168-174, and 178-185 are under examination. Claims 116 and 164 are amended. Claims 132-137, 142-145, 152-159, 161-163, 167, and 175-177 are withdrawn from consideration. It is Applicant's understanding that if the elected subject matters is found to be allowable over the prior art, the search and examination will be expanded to cover other species until it includes the full scope of the generic claims. After entrance of the amendments, claims 116-131, 138-141, 146-151, 160, 164-166, 168-174, and 178-185 will be pending and under examination.

Support for the amendments to claims 116 and 164 can be found in the claims as filed. These amendments add no new matter.

Claim amendments are for purposes of improved clarity or consistency of claim language unless otherwise noted. No claim amendment should be construed as an acquiescence in any ground of rejection.

Double Patenting Rejections

Claims 116-131, 138-141, 146-151, 160, 164, 168-174, and 178-185 stand rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent Nos. 6,443,898, 6,416,740, and 6,403,056. Applicant respectfully requests that these rejections be reconsidered in light of the claim amendments submitted herein. Should any of these rejections be maintained, Applicant proposes to file a terminal disclaimer as provided in 37 C.F.R. § 1.130(b) once the Examiner has issued a favorable ruling indicating that the amended claims will be allowed. Applicant will be filing the terminal disclaimers to facilitate prosecution and expresses no opinion as to whether the obviousness-type double patenting rejection is warranted in view of the aforementioned patents.

Claims 116-131, 138-141, 146-151, 160, 164, 168-174, and 178-185 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims of copending Application No. 09/075,477, 09/218,660, 09/813,484 and 10/055,772. Applicant respectfully requests that this rejection also be reconsidered in light of the claims amendments submitted herein. Should the rejection over the copending applications be maintained, Applicant reserves the right to address such rejections once claims are allowed in those applications.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 116-185 stand rejected with respect to recitation of the term "enhancing". According to the Action, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant respectfully traverses and directs the Examiner's attention to pages 87-90 of the specification. On these pages, Applicant teaches how to determine the amount of bioactive agent delivered to a tissue by determining blood flow within a target zone, the concentration of bioactive agent in the blood at the site of ultrasound administration, and the efficiency of delivery as a result of the use of ultrasound. Using the formulas set forth in the specification, a skilled practitioner could routinely determine the amount of bioactive agent delivered to the tissue using the methods of the present invention and compare it to the amount of bioactive agent delivered to the tissue using known methods. By comparing the two numbers, the skilled practitioner could then determine whether the methods of the present invention enhance delivery of the bioactive agent to the tissue. Applicant therefore respectfully requests that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. § 102(b)

Claims 116-131, 138-140, 160, 164-166, 168-174, and 178-184 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Siegel (U.S. Patent No. 5,695,460). According to the Examiner, Siegel's delivery of thrombolytics to vascular ischemic tissues anticipates the limitations of the instant claims. The Applicant respectfully traverses for at least the following reasons.

First, the Siegel reference neither expressly nor inherently sets forth the element that the gaseous vesicles or acoustically active compositions be administered to a patient by ***continuous*** infusion. Second, the Siegel reference provides no indication that the disclosed methods provide delivery of the thrombolytic agent to a selected tissue, or that ultrasound enhances such delivery.

For a rejection under § 102(b) to be properly founded, a single prior art reference must disclose, either expressly or inherently, each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In *Scripps Clinic & Research Found. v. Genetech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the presently claimed invention.

The rejection cites Siegel as the basis for the § 102(b) rejection yet fails to identify any disclosure or suggestion in Siegel to administer a gaseous vesicle or acoustically active composition by continuous infusion. In fact, the Action does not even appear to recognize that independent claims 116 and 164 recite this claim element.

Furthermore, the Action fails to recognize that the present claims recite that ultrasonic energy be applied in an amount sufficient to produce cavitation or rupture of the vesicles or in an amount sufficient to activate an acoustically active composition. The Action cites *In re Hutchinson*, 69 USPQ 138, for the proposition that the terms "sufficient" or "capable" to perform a given function are not positive limitations but only require the ability to so perform. Hutchinson, however, does not stand for the proposition that terms such as "sufficient" or "capable" cannot constitute limitations in a patentable sense but instead, for the proposition that functional statements cannot not limit article claims. The present claims are method claims, not article claims, and as such, can be limited by functional statements. The present application specifically describes how to ensure enhanced delivery of a bioactive agent to a tissue by optimizing both ultrasound frequency and the depth of penetration and the theoretical volume of insonation provided by the ultrasound transducer used (see pages 88-91 of the specification). Although the Siegel reference may be deemed to teach that the co-administration of ultrasound and a contrast agent, when combined with a thrombolytic agent, can enhance thrombolysis, Siegel completely fails to provide a description of the application of ultrasound *in an amount sufficient* to achieve such a result, as instantly claimed. It is evident from the Seigel specification that administering the amount of ultrasonic energy necessary to delivery a bioactive agent into a selected tissue is not even contemplated. For example in column 5, lines 17-28, Siegel teaches that it is necessary to

introduce the echo contrast agent into the vessel at a *position proximate* to the thrombosis in order to ensure that the agent will even reach the thrombosis!

Moreover, as discussed in a previous amendment, Siegel explicitly *teaches away* from the application of ultrasound at the frequency recited in Claim 164 and in Claim 185. In this regard, Siegel states:

> Importantly, it has been found that when ultrasound is applied at a lower, rather than a higher frequency, the effectiveness of the method is markedly enhanced. More particularly, when ultrasound is applied at *less than about 100 kHz*, and even more particularly, between approximately 25 kHz and approximately 53 kHz, the dissolution of thrombi is most significant.

See Siegel, col. 5, lines 29 to 35 (emphasis added).

It is thus clear that Siegel fails to teach or suggest the following:

- application of ultrasound for the purposes claimed by Applicant;
- the application of ultrasound in an amount sufficient to achieve enhanced delivery of the bioactive agent from the vasculature into a selected tissue; and
- the application of ultrasound energy having a frequency of from 100 kHz to 1MHz.

Indeed, with regard to this latter element, as discussed above, Siegel *teaches away* from the defined ultrasound frequencies. In particular, as noted above, Siegel teaches the use of ultrasound frequencies of less than about 100 kHz, preferably from 25 kHz to about 53 kHz.

Accordingly, the Applicant respectfully submits that the rejection of the claims under §102(b) be withdrawn.

Rejections under 35 U.S.C. § 102(e)

Claims 116-131, 138-141, 146-151, 160, 164, 168-174, and 178-184 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Unger (U.S. Patent No. 6,443,898), Klaveness (U.S. Patent No. 6,331,289), and Schneider (U.S. Patent No. 6,258,378).

In response, the Applicant respectfully traverses the rejections for at least the following reason. The present claims are directed to methods for enhancing delivery of a bioactive agent from the vasculature to a selected tissue in a patient comprising three separate steps, *e.g.*, administering a bioactive to a patient, administering a vesicle composition or acoustically active composition to the patient, and applying ultrasound to the patient. Accordingly, in the present claims, the bioactive agent is not contained within the vesicle or acoustically active composition. In contrast, in the cited references, the bioactive agent is contained within the gas containing compositions. Thus, the cited references cannot be said to anticipate the present invention and the Applicant respectfully requests that the rejections under § 102(e) be withdrawn.

First Rejection under 35 U.S.C. § 103

Claims 141, 146-151, and 185 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Siegel (U.S. Patent No. 5,695,460).

In this rejection, the Examiner alleges that Siegel teaches the method steps of the instant claims and, accordingly, absent a showing of unexpected results, modifying the rate of infusion of the gas-filled compositions and the ultrasound frequency would have been achieved by routine experimentation. Applicant respectfully traverses.

As explained in the MPEP, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the

references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, not in Applicants disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The rejection fails for at least the following reasons. First, the Siegel reference neither suggests nor motivates the method claims of the present invention. Second, there is not a reasonable expectation of success. Third, the Siegel reference neither teaches nor suggests all the claim limitations.

The Applicant has found that administering a gaseous composition or acoustically active composition to a patient by continuous infusion enhances delivery of a bioactive agent from the vasculature into a selected tissue of a patient. The claims recite both that the gaseous composition or acoustically active composition be administered to a patient by continuous infusion and that ultrasonic energy be applied in a sufficient amount to deliver a bioactive agent to a selected tissue. In contrast, the Siegel patent requires that an echo contrast agent containing microbubbles be delivered to the *vasculature* of a patient. The Siegel patent is directed to methods of dissolving arterial thrombi. Accordingly, the Siegel patent requires that the contrast agent be delivered to the vasculature, *not to tissue.* Because the continuous intravascular infusion methods of the present invention enhance delivery of a bioactive agent from the vasculature to a selected tissue, there would be no reason to modify the teachings of Siegel to provide for improved administration of a bioactive agent from the vasculature into a selected tissue as described in the present application.

In addition, there is no reasonable expectation of success based on the teachings of Siegel that administration of the gaseous compositions or acoustically active compositions by continuous infusion in accordance with the methods of the present invention would have the effect of enhancing delivery of a bioactive agent to a selected tissue because Siegel makes no suggestion of this result.

Finally, the prior art reference much teach or suggest all of the limitations of the claims in order establish a *prima facie* case of obviousness. Applicant asserts that the cited reference does not suggest all of the limitations of the claims and therefore, the obviousness rejection is untenable. The Applicant claims a method of increasing delivery of a bioactive agent from the vasculature into a selected tissue. The Siegel reference does not teach delivery of a bioactive agent to a tissue. Moreover, the Siegel reference does not teach administration by continuous infusion.

Accordingly, the Applicant respectfully requests that the rejection of the claims over Siegel be withdrawn.

Second Rejection under 35 U.S.C. § 103

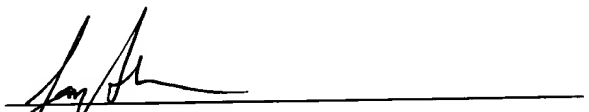
Claims 116-131, 138-141, 146-151, 160, 164-166, 168-174 and 178-184 stand rejected as allegedly obvious over Porter (U.S. Patent No.5,648,098) in view of Siegel. The Examiner alleges that the combined teachings of Porter and Siegel suggest the use of a ultrasonic gaseous contrast agent with a therapeutic agent to improve the therapeutic end result. The Applicant respectfully traverses.

As previously discussed, Siegel discloses methods of delivering a contrast agent to a blood vessel in order to dissolve arterial thrombi. Like Siegel, Porter is directed to thrombolytic therapy. Porter differs from Siegel in that it discloses the use of a medicament

in addition to a contrast agent in order to dissolve arterial thrombi. Like Siegel, Porter does not contemplate the delivery of bioactive agents into tissues, *but into blood vessels*. Accordingly, neither reference cited by the Action discusses delivery of a bioactive agent from the vasculature into a tissue and consequently, neither reference can render obvious the present claims.

In conclusion, the Action provides no showing as to what in the cited references would motivate one of skill to deliver a bioactive agent from the vasculature to a selected tissue using the methods of the present invention. Accordingly, the Applicant respectfully requests that the rejections under 35 U.S.C. § 103(a) be withdrawn.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicant submits that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested.



Leslie E. Aberman
Limited Recognition Under 37 CFR§ 10.9(b) attached

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

APPENDIX A
VERSION WITH MARKINGS TO SHOW CHANGES MADE TO THE CLAIMS

116. (Thrice amended) A method for enhancing the delivery of a bioactive agent from the vasculature to a selected tissue in a patient, said method comprising:

(i) administering said bioactive agent to said patient;

(ii) administering a vesicle composition to said patient, by continuous intravascular infusion, wherein said vesicle composition comprises, in an aqueous carrier, vesicles comprising lipids, proteins, or polymers and a gas or gaseous precursor; and

(iii) applying ultrasonic energy to the patient in an amount sufficient to produce cavitation or rupture of said vesicles, and sufficient to increase delivery of said bioactive agent from the vasculature into said selected tissue, wherein said bioactive agent is delivered into said selected tissue.

164. (Thrice amended) A method for enhancing the delivery of a bioactive agent from the vasculature to a selected tissue in a patient, said method comprising:

(i) administering said bioactive agent to said patient;

(ii) administering an acoustically active composition to said patient, by continuous intravascular infusion; and

(iii) applying ultrasonic energy to the patient in an amount sufficient to activate said acoustically active composition, and sufficient to increase delivery of said bioactive agent from the vasculature into said selected tissue, wherein said bioactive agent is delivered into said selected tissue and said ultrasound energy has a frequency of from about 100 kHz to about 1 MHz.